NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document** from Janssen

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. EGFR Positive
   b. Roy Castle Lung Cancer Foundation

4. **Evidence Review Group critique of company comments on the ACD**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Patient group	EGFR Positive UK	Unmet need - this is massive and should have been much more strongly registered.	Comment noted. The committee acknowledge the unmet need for more effective treatment options that specifically target exon 20 insertion mutations (see FAD section 3.1). The views of clinical experts and patient/carer representatives were considered by committee when formulating its recommendations (see FAD section 3.1).
2	Patient group	EGFR Positive UK	Small population who are greatly underserved and are outliers in the EGFR community	Comment noted. The committee acknowledge the unmet need for more effective treatment options that specifically target exon 20 insertion mutations (see FAD section 3.1). The views of clinical experts and patient/carer representatives were considered by the committee when formulating its

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				recommendations (see FAD section 3.1).
3	Patient group	EGFR Positive UK	The negative impact of knowing a treatment is available and not being able to access it. Both drugs are approved and used in other countries yet in the UK patients with Exon 20 ins are denied this opportunity	Comment noted. The committee makes recommendations based on the cost-effectiveness of therapies specific to clinical practice in England. Considerations about cost effectiveness are explained in the Guide to the methods of technology appraisal section 6.2.13–6.2.19.
4	Patient group	EGFR Positive UK	In the absence of a well known and followed standard of care these patients, whose diagnosis is often missed, are placed on a variety of treatment pathways which have limited efficacy and often have a high toxicity.	Comment noted. The committee acknowledge the unmet need for more effective treatment options that specifically target exon 20 insertion mutations (see FAD section 3.1).
5	Patient group	EGFR Positive UK	The emotional, social and economic impact on quality life when living with EGFR Positive lung cancer has not been registered	Comment noted. The views of clinical experts and patient/carer representatives were considered by the committee when formulating its recommendations see FAD section 3.1). NICE expects its advisory bodies to use their scientific and clinical judgement in deciding whether the available evidence is

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				sufficient to provide a basis for recommending or rejecting particular clinical or public health measures (Social Value Judgements; 'Principles for the development of NICE guidance', principle 1). Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 2).
6	Patient group	EGFR Positive UK	The positive impact of having access to a targeted therapy that prolongs their life and positively impacts the quality of their life. This treatment is a game changer for these patients and not enough emphasis has been made of this.	Comment noted. The committee recognise that amivantamab is innovative and represents a step-change in the treatment of exon 20 insertion mutation-positive NSCLC (see section 3.20). Following the first committee meeting, the company presented

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				evidence to indicate that there were additional benefits that were not captured in the QALY calculations. The committee considered this additional information but concluded that there were not any additional benefits that had not been captured in the QALY calculations (see FAD section 3.20).
7	Patient group	Roy Castle Lung Cancer Foundation	We are disappointed that the Appraisal Committee Decision is not to recommend this therapy in this indication. This would be the first to be NICE recommended for treating this highly selected group of patients, with EGFR exon 20 insertion mutation-positive, advanced non small cell lung cancer. As acknowledged in the ACD, indirect comparisons using real world evidence suggest that amivantamab, in this indication, increases how long people live and how long before their cancer gets worse. This is of obvious importance in this patient group. As further acknowledged, this therapy does meet the criteria of a life extending treatment, at end of life. These patients do not have time to wait. As such, we would encourage discussion with the manufacturer around cost and potential for use in the Cancer Drugs Fund, whilst further data becomes available.	Comment noted. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). As the main uncertainties in this appraisal related to the limitations of the company's approach to existing real-world evidence (see FAD section 3.5 and section 3.6) and because CHRYSALIS was mature, making amivantamab available in the Cancer Drugs Fund would be unlikely to reduce the uncertainties in the appraisal. Therefore, the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				committee concluded that amivantamab could not be recommended for use in the Cancer Drugs Fund (see FAD section 3.19).
8	Company	Janssen	**Executive summary** Janssen welcome the opportunity to comment on the preliminary recommendation made by the appraisal committee (AC) detailed in the appraisal consultation document (ACD) for amivantamab for treating epidermal growth factor receptor exon 20 insertion mutation-positive (EGFR Exon20ins) advanced non-small-cell lung cancer (NSCLC) after platinum-based chemotherapy. Whilst Janssen are disappointed that the AC's preliminary decision is to not recommend amivantamab within its marketing authorisation, we are, however, committed to working with the National Institute for Health and Care Excellence (NICE) to address the AC's key concerns, as outlined in the ACD, to enable patients to access to this innovative and clinically beneficial treatment. Janssen would like to re-iterate the unmet need that patients with locally advanced or metastatic NSCLC with EGFR Exon20ins face. Life expectancy in patients with EGFR Exon20ins is shorter than in patients with common EGFR mutations. This is, in part, because there currently are no NICE recommended treatments that specifically target the EGFR Exon20ins mutation. Both patient and clinical experts have highlighted that this is a condition that has a substantial impact on the quality of life of patients and that of their caregivers and has an immense unmet need for targeted therapies such as amivantamab, in the absence of effective standard of care (SoC) treatments. This is also acknowledged by the NICE Committee in the ACD (page 5): *"The committee concluded that there is an unmet need for more effective treatment options that specifically target the exon 20 insertion mutations."* Further, Janssen considers that there are a number of benefits of amivantamab that are not captured in the cost per quality-adjusted life year (QALY) calculations	Comments noted. See detailed responses below.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			that should be taken into account for committee decision making: • Amivantamab provides benefits aligned with patient preferences including the value of hope associated with a treatment that improves survival outcomes • Patients place more value on later line treatments such as amivantamab given the effects of stigmatisation within NSCLC in delaying treatment seeking behaviours and thus NICE should consider the stigma as a social value judgement issue. • Amivantamab would alleviate both patient and caregiver burden associated with EGFR Exon20ins mutated NSCLC. Janssen have provided a response which focusses on areas of uncertainty that were identified by the AC, with a particular focus on the provision of information (such as the completion of the DataSAT Checklist) to further reassure the AC that the real-world evidence (RWE) analyses informing the efficacy of UK SoC in the submission are robust, reliable, and fit for purpose. Overall, this response covers the following points: • The reporting of the real-world evidence for the comparator arm • The stigma associated with EGFR Exon20ins NSCLC • The most appropriate approach for amivantamab time on treatment • The addition of a scenario exploring the impact of diagnostic testing costs • Revised base case cost-effectiveness analysis and revised PAS • Benefits not captured within the cost per QALY framework • Factual inaccuracies • Confidentiality highlighting errors As indicated in the bullet points above, a revised PAS has been included as part of this response, representing a [redacted] discount on the list price of amivantamab.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
9	Company	Janssen	**The reporting of the real-world evidence for the comparator arm** Page 9 of the ACD states: *"the committee considered that the company had not provided enough information on data provenance, data accuracy and data suitability, and had not explored the effect of missing data. The committee concluded that the way the company had chosen and used real-world evidence was associated with several areas of uncertainty."* As per the original submission, and as noted by the AC, due to the single arm nature of the CHRYSALIS trial and the rarity of EGFR Exon20ins-mutated NSCLC, RWE is the most appropriate available source of comparator efficacy evidence and demonstrates that amivantamab is associated with a consistent and statistically significant treatment benefit when compared to current SoC treatments across all endpoints. However, to address the uncertainty highlighted by the evidence review group (ERG) and AC in the ACD, Janssen have provided additional information below regarding the use of RWE within the submission. • *"The committee noted that the company could have used well-validated real-world evidence checklists and reporting tools (such as the RECORD-PE checklist or the STaRT-RWE template)."* Janssen have now completed the DataSAT checklist, as recommended by the NICE RWE framework.[1] This is provided in Appendix 2 of this response. • *"The company could have done a sensitivity analysis using a multiple imputation approach to assess the impact of missing data."* Janssen have now conducted sensitivity analyses assessing the impact of missing data on the indirect analyses informing the comparison of amivantamab versus UK SoC utilising US RWE. The following analyses have been conducted: • Amivantamab versus pooled US RWE with imputation for missing values • Amivantamab versus pooled US RWE with imputation for missing values and with EGFR tyrosine kinase inhibitors (TKIs) excluded • Amivantamab versus Flatiron with imputation for missing values	Comment noted. The committee acknowledged the additional information provided by the company. Overall, the committee concluded that some areas of uncertainty remained and some of this uncertainty was currently unresolvable. It noted that the level of uncertainty could have been reduced if the company had shown that a systematic approach had been taken to selecting real-world evidence sources (see FAD section 3.5).

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
Amivantamab versus Flatiron with imputation for missing values and with EGFR TKIs excluded
ConcertAI did not have any missing values and therefore a multiple imputation approach was not required to be investigated in a sensitivity analysis. Whilst COTA did have some missing values (for number of metastatic locations), adjusting for all covariates including this covariate led to a large degree of imbalance; therefore, only covariates up to and including Eastern Cooperative Oncology Group performance status (ECOG PS) were adjusted for. Therefore, results with imputation do not apply to COTA.

The results of these analyses are presented in Error! Reference source not found. of Appendix 3 below. Analyses of amivantamab versus each US source individually with and without the exclusion of EGFR TKIs are also presented in Appendix 3 without consideration of the imputation of missing values, in line with the base case approach from the Company Submission. Overall, the results demonstrate consistency across endpoints and data sources irrespective of the application of imputation and/or the inclusion/exclusion of EGFR TKIs.

“It could also have reduced uncertainty by providing further detail on how it chose data sources and assessed their suitability. In particular, for each of the 3 US real-world evidence sources in the company base case, further information to reduce uncertainty could have included:
a description of each data source and the number of people included”
Information on the eligibility criteria for each US data source can be found in Table 1 below.

Table 1: Eligibility criteria for each US data source
<table>
<tr><th>ConcertAI</th><th>COTA</th><th>Flatiron</th></tr>
<tr><td colspan="3">Inclusion criteria:</td></tr>
<tr><td>• Aged ≥18 years at the time of Stage</td><td>• NSCLC
• Confirmed EGFR</td><td>• ICD code for lung cancer (ICD-9-CM</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th colspan="3">Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td colspan="3"><table>
<tr><td>IIIB, IIIC, or IV NSCLC diagnosis
• Pathology consistent with NSCLC
• Stage IIIB, IIIC, or IV NSCLC, either at the time of their initial NSCLC diagnosis or after development of recurrent or progressive disease
• Documented EGFR Exon20ins result at any time after their initial NSCLC diagnosis</td><td>Exon20ins</td><td>• 162.x, ICD-10 C34x, C39.9)
• ≥2 documented clinical visits in the Flatiron EHR on or after 1/1/2011
• Abstractor-confirmed pathology consistent
• with NSCLC
• Diagnosed with Stage IIIB, IIIC, IVA, or IVB NSCLC on or after 1/1/2011 or early stage NSCLC that later developed into abstractor-confirmed, recurrent or progressive disease on or after 1/1/2011
• Received ≥1 line of therapy in the advanced NSCLC setting
• Positive EGFR Exon20ins result at any time</td></tr>
<tr><td colspan="3">Exclusion criteria:</td></tr>
<tr><td>• Insufficient EHR data</td><td>• Multiple concurrent primary cancer diagnoses, or not actively treated at 1 of the 5 sites, or had</td><td>• No records of visits or medication orders in the EHR in the 90 days after their abstracted</td></tr>
</table></td><td></td></tr>
</table>

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	insufficient EHR data	advanced NSCLC diagnosis date

Abbreviations: CM: clinically modified; EGFR: epidermal growth factor receptor; EHR: electronic health record; Exon20ins: exon 20 insertion mutations; ICD: International Statistical Classification of Diseases and Related Health Problems; LOT: line(s) of therapy; NSCLC: non-small cell lung cancer.

The methodology by which the lines of treatment (LOTs) ultimately used in the adjusted analysis were derived is presented in Table 1 of Minchom *et al.* (2022; see **Error! Reference source not found.**, Appendix 1).[2] Additionally, in the analysis informing this submission specifically, exclusion of LOTs for patients who were not diagnosed with NSCLC with EGFR Exon20ins at the time of LOT start was conducted, leading to [redacted] patients representing [redacted] LOTs.

- *"a description of the provenance of the data source"*

Further information on data provenance can be found in the DataSAT checklist provided in Appendix 2.

- *"further information on key study variables and outcomes, including details on data availability and completeness, how they were measured and derived from the data, whether any linkage to external data sources was included and an assessment of accuracy"*

Further information on key study variables and outcomes can be found in the DataSAT checklist provided in Appendix 2.

- *"a description of the missing data and the number of people excluded from the analyses at each step of filtering (for example, how many people were filtered because of each eligibility criterion or because of missing data on key confounding variables)"*

As described above, details regarding patient disposition from the US RWE sources can be found in Table 1 of Minchom *et al.* (2022; see **Error! Reference**

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			source not found., Appendix 1), including the number of LOTs excluded at each stage of the analysis for both the pooled US data set and each contributing source individually.[2] Additionally, a further criteria was applied for the analysis informing the Company Submission: exclusion of LOTs for patients who were not diagnosed with NSCLC with EGFR Exon20ins at the time of LOT start, meaning that [redacted] LOTs were included in the final analysis set of interest. Missing data for baseline demographics and clinical characteristics for the US RWE sources (pooled and by source) can be found in Table 2 of Minchom *et al.* (2022; see **Error! Reference source not found.**, Appendix 1) for Race, smoking history and ECOG performance status.[2] Race and smoking history were not included as covariates in the adjusted analyses (reasons for this are described in Table 59 of the Company Submission appendices). Additionally, data were missing from Flatiron [redacted] and COTA [redacted] for the covariate of 'number of metastatic locations'. Sensitivity analyses utilising a multiple imputation approach to account for these missing data are presented in **Error! Reference source not found.**. o *"the time period when the information was collected for each variable in the real-world evidence, defined in relation to the treatment start date."* Further information on the time frame of data collection can be found in the DataSAT checklist provided in Appendix 2. • *"The committee also noted that a full study protocol for each of the real-world evidence sources according to the NICE real-world evidence framework requirements should be provided."* The study protocol for the RWE study comparing CHRYSALIS to the three US data sources is included in the reference pack.[3]	
10	Company	Janssen	**The most appropriate approach for amivantamab time on treatment**	Comments noted. The

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			Janssen maintain that the most appropriate approach to model time on treatment for amivantamab is via treat-to-progression as per marketing authorisation. Janssen wish to emphasise that UK-based clinicians stated that patients would discontinue treatment with amivantamab upon experiencing a progression event, and thus we maintain that the assumption that time to treatment discontinuation (TTD) is equal to progression-free survival (PFS) is appropriate. In addition, it is important to note that patients in clinical trials are monitored more closely than in the real world and as such, progression in CHRYSALIS would have been detected earlier than it would in real-world clinical practice. Progression is not a hard stop, rather it evolves at the cellular level before impacting patient health-related quality of life (HRQoL). Therefore, the use of early detected progression to inform HRQoL may underestimate the benefit of amivantamab. However, in acknowledgement of the concerns of the ERG and AC regarding this assumption, a scenario based on the revised base case exploring the Gompertz curve choice for amivantamab TTD is also presented as a scenario analysis. The rationale for this selection, rather than the use of the Exponential, is described below. In the ACD, the AC state that *'It is appropriate to base time on treatment on CHRYSALIS time to treatment discontinuation data, extrapolated using the exponential curve'*. Whilst the company understand that the ERG and AC prefer the use of TTD data from CHRYSALIS, Janssen disagree with this statement. If the use of TTD is to be taken forward, then the Exponential curve is not the most appropriate curve choice to select. As previously described by the company, although the Exponential curve has the best statistical fit, the Gompertz or Weibull curves are more appropriate selections as statistical fit is not the only consideration of relevance when selecting the most appropriate curve. Additionally, when considering the TTD extrapolation for amivantamab (see Figure 1), statistical fit might not be the most reliable measure, because the fit at the start of the Kaplan-Meier is very similar between curves and only towards the end of the timeframe does it diverge. At later timepoints, there are fewer patients at risk so the statistical fit to the Kaplan-Meier is less relevant.	committee discussed the company's and ERG's preferred approaches for modelling time on treatment and the relative merits/drawbacks of each (see FAD sections 3.12 and 3.13). Overall, the committee concluded that selecting the Gompertz curve for modelling the time to treatment discontinuation data was appropriate, but noted that scenario analyses using the exponential curve should also be considered in decision-making.

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			Figure 1: Amivantamab TTD extrapolations and Kaplan-Meier data  **Abbreviations:** TTD: time to treatment discontinuation; KM: Kaplan-Meier. Further, as previously described, the Gompertz is most aligned with smoothed hazard curve for TTD (see Figure 2 below). The Exponential curve assumes constant hazards over time, which is not aligned with the hazards demonstrated for amivantamab TTD. The relationship to PFS can also be considered in selecting an appropriate curve for TTD. When assessing this relationship, for the Exponential curve, patients remain on treatment beyond progression, and the difference between TTD and PFS is particularly prominent towards the tail of the extrapolations. For both Gompertz and Weibull, patients remain on treatment beyond progression but the difference is not as prominent and is more aligned throughout with a narrowing at the tail (see Figure 3). **Figure 2: CHRYSALIS TTD – smooth and unsmoothed**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **Abbreviations**: TTD: time to treatment discontinuation. **Figure 3: Relationship between TTD and PFS with the Exponential and Gompertz extrapolations**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			[redacted] **Abbreviations**: KM: Kaplan-Meier; OS: overall survival; PFS: progression-free survival; SoC: standard-of-care; TTD: time to treatment discontinuation. The results of a scenario analysis implementing a Gompertz selection for amivantamab TTD is presented in Table 2 below. **Table 2: Deterministic scenario analysis results – amivantamab ToT=TTD (Gompertz)**	

	LIST PRICE			WITH PAS		
	Incr. costs (£)	**Incr. QALYs**	**ICER (£/QALY)**	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£/QALY)**
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,766
Amivantamab ToT=TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,091

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>(Gompertz)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; Incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years.
</td><td></td></tr>
<tr><td>11</td><td>Company</td><td>Janssen</td><td>
The addition of a scenario exploring the impact of diagnostic testing costs

As requested by the AC, Janssen have conducted a scenario analysis exploring including the cost of testing for EGFR Exon20ins in NSCLC at £550 per patient with NSCLC with EGFR Exon20ins. The results of this scenario analysis are presented in Table 3 below based on the updated base case (see Section 5) and demonstrate that the addition of the testing costs marginally increases the with-PAS ICER from [redacted].

Table 3: Deterministic scenario analysis results – inclusion of diagnostic testing costs
<table>
<tr><th rowspan="2"></th><th colspan="3">LIST PRICE</th><th colspan="3">WITH PAS</th></tr>
<tr><th>Incr. costs (£)</th><th>Incr. QALYs</th><th>ICER (£/QALY)</th><th>Incr. costs (£)</th><th>Incr. QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>Base case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£27,766</td></tr>
<tr><td>Inclusion of testing costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£28,733</td></tr>
</table>
Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; Incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years.
</td><td>Comments noted. The committee considered the scenario provided by the company and concluded that diagnostic testing costs should be included in the amivantamab arm of the economic model (see FAD section 3.15).</td></tr>
<tr><td>12</td><td>Company</td><td>Janssen</td><td>
Revised base case cost-effectiveness analysis and revised PAS

Janssen present a revised company base case, accommodating the following assumptions as preferred by the AC:
• excluding EGFR TKIs from the blended comparator arm
• using the inverse probability weighting method for the indirect
</td><td>Comment noted. The committee considered the updated company base-case, which incorporated the majority of the committee’s preferred</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
treatment comparison
• using utility values from TA713
• using parametric modelling to represent survival in the blended comparator arm
• excluding treatment waning

This base case assumes that time on treatment for amivantamab equals PFS for the reasons described in Section 3. A scenario analysis considering TTD data for amivantamab (Gompertz) is presented in Table 2 above.

The revised base-case deterministic and probabilistic cost-effectiveness analyses are presented in Table 4 and Table 5 below. As mentioned in the executive summary, the PAS for amivantamab has been updated. ‘With PAS’ results incorporate this new discount.

Table 4 Updated base case results at amivantamab PAS price (deterministic)
<table>
<tr><th></th><th colspan="3">Total</th><th colspan="3">Incremental</th><th rowspan="2">ICER (£/QALY)</th></tr>
<tr><th></th><th>Costs</th><th>QALYs</th><th>LYs</th><th>Costs</th><th>QALYs</th><th>LYs</th></tr>
<tr><td>UK SoC</td><td>[redacted]</td><td>[redacted]</td><td>1.35</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>AMI</td><td>[redacted]</td><td>[redacted]</td><td>2.27</td><td>[redacted]</td><td>[redacted]</td><td>0.92</td><td>£27,766</td></tr>
</table>
Abbreviations: AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

Table 5: Updated base case results at amivantamab PAS price (probabilistic)
<table>
<tr><th></th><th colspan="3">Total</th><th colspan="3">Incremental</th><th rowspan="2">ICER (£/QALY)</th></tr>
<tr><th></th><th>Costs</th><th>QALYs</th><th>LYs</th><th>Costs</th><th>QALYs</th><th>LYs</th></tr>
<tr><td>UK SoC</td><td>[redacted]</td><td>[redacted]</td><td>1.36</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
</td><td>assumptions from ACM1 and the revised Patient Access Scheme discount. Once diagnostic testing costs were added, all of the ICER were above the range considered to be a cost-effective use of NHS resources (see FAD section 3.18).</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			AMI | [redacted] | [redacted] | 2.28 | [redacted] | [redacted] | 0.92 | £28,909 **Abbreviations:** AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.	
13	Company	Janssen	**Benefits not captured within the cost per QALY framework** As described in the Executive Summary, there are a number of benefits of amivantamab which are not explicitly captured in the QALY calculation, which, if included, would improve the cost-effectiveness of amivantamab further. The impact of stigma on delayed diagnosis and treatment is described in detail in Section 2; however, additional considerations beyond this are elaborated upon here. Providing benefits which are aligned to patient and caregiver preferences are not considered in the QALY framework. The extended period progression-free or alive associated with amivantamab versus UK SoC may reduce the anxiety associated with progression or death observed in both patients and carers. Prolonged time progression-free may also lead to improvement in aspects of daily life most valued by patients, such as being able to undertake daily activities, maintaining independence and 'feeling normal' (as described in Section B.1.3.1 of Document B), the value of which is not intrinsically captured in the QALY framework. Further, patients become frustrated when they are told that although they have an EGFR positive mutation, that their particular mutation cannot be treated with EGFR TKIs. Therefore, the value of hope associated with receiving a targeted treatment for NSCLC with EGFR Exon20ins is incredibly high and is also not intrinsically captured. In addition, patients with NSCLC with EGFR Exon20ins have a poorer prognosis than other patients with common EGFR mutations where there is a larger degree of treatment choice with a proven benefit.[6] Therefore, this also supports that there is additional value in amivantamab being available to patients as an additional treatment option for use by oncologists beyond the limited treatment options for these patients compared	Comment noted. Committee considered the information provided by the company. They recognised that there is stigma associated with a lung cancer diagnosis, unmet need for targeted treatment options and poor prognosis. They acknowledged the significant emotional burden that a diagnosis of lung cancer has for people and their caregivers. The committee felt that the benefits highlighted by the company would be captured within the EQ-5D tool which underpins the QALY calculations (see FAD section 3.20). They noted that the poor prognosis and lack of treatment options was reflected by the end of life weighting being applied to the maximum acceptable ICER (see section 3.15).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			with those for patients with EGFR common mutations. In-depth interviews with patients with NSCLC with EGFR Exon20ins have revealed that patients anticipate negative views from others and are reluctant to share their diagnosis with their employers and wider society for fear of being seen as responsible for their illness. Many patients have experienced unfair treatment due to their diagnosis, with 55% having experienced stereotypes about people who have lung cancer and 28% have experienced prejudice towards people with lung cancer. Given the benefits that amivantamab may bring as compared to the current UK SoC, this may lead to alleviation of stigma, which would not be captured in generic QoL measures and therefore in QALY calculations.[5] Additionally, for those living with NSCLC with EGFR Exon20ins, anticipated stigma can impact their ability to work as they do not want to be judged or excluded in the work setting. Some patients that were interviewed spent so much time worrying about work, the opinions of their colleagues and their financial situation that this ultimately contributed to feeling they needed to stop working due to the emotional strain. This was further shown in the quantitative survey conducted in EGFR+ patients with 35% worrying or experiencing discrimination in the workplace.[5] The inextricable link between stigma and discrimination in the workplace in those that were sampled demonstrates that stigma may have productivity implications for some patients. Any benefits in terms of the alleviation of this indirect economic burden would not be captured within the economic model.	They considered the unmet need and the burden of stigma in their deliberations, but concluded that there were no additional benefits which had not been captured in the QALY calculations.
14	Company	Janssen	**Factual inaccuracies** • Page 9 of the ACD states *"In contrast, the NCRAS evidence only provided data on time to next treatment and overall response rate."* Janssen would like to clarify that the NCRAS (Public Health England [PHE]) data source only provided data on time to next treatment and **overall survival**. Overall response rate data were not available from the NCRAS data set.	Comment noted. The items have been corrected in the FAD (see FAD sections 3.4 and 3.5).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• Janssen would like to clarify a misunderstanding around why updated efficacy analyses from the n=153 population could not be provided; as noted on Page 7 of the ACD. The AC noted that Janssen did not provide a reason for why efficacy analyses for this population were not presented. The n=153 population included all patients with NSCLC with EGFR Exon20ins who received prior chemotherapy at the recommended Phase 2 dose (RP2D) prior to the 30 March 2021 data cut-off. However, the n=114 efficacy population included all patients with NSCLC with EGFR Exon20ins who received the RP2D prior to 04 June 2020 data cut-off with **≥3 disease assessments** as of the 08 October 2020 data cut-off. This difference in the populations means that efficacy data are not available for the larger n=153 population as not all patients in the safety population had received **≥3 disease assessments** to be considered for an efficacy analysis set.	
15	Company	Janssen	**Confidentiality highlighting errors** • Page 12 of the ACD states the number of patients that EuroQoL-5 dimensions-5 levels (EQ-5D-5L) data were collected within the CHRYSALIS trial without academic in confidence highlighting. This should be amended as follows: *"The company explained that EQ-5D-5L data from the CHRYSALIS trial was collected for only* [redacted] *people, and only for the progression-free survival state."*	Comment noted. The academic in confidence number has been retrospectively removed from the ACD and has not been included in the FAD.

NICE National Institute for Health and Care Excellence

Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 16 September 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Janssen-Cilag Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Executive summary Janssen welcome the opportunity to comment on the preliminary recommendation made by the appraisal committee (AC) detailed in the appraisal consultation document (ACD) for amivantamab for treating epidermal growth factor receptor exon 20 insertion mutation-

positive (EGFR Exon20ins) advanced non-small-cell lung cancer (NSCLC) after platinum-based chemotherapy.

Whilst Janssen are disappointed that the AC's preliminary decision is to not recommend amivantamab within its marketing authorisation, we are, however, committed to working with the National Institute for Health and Care Excellence (NICE) to address the AC's key concerns, as outlined in the ACD, to enable patients to access to this innovative and clinically beneficial treatment.

Janssen would like to re-iterate the unmet need that patients with locally advanced or metastatic NSCLC with EGFR Exon20ins face. Life expectancy in patients with EGFR Exon20ins is shorter than in patients with common EGFR mutations. This is, in part, because there currently are no NICE recommended treatments that specifically target the EGFR Exon20ins mutation. Both patient and clinical experts have highlighted that this is a condition that has a substantial impact on the quality of life of patients and that of their caregivers, and has an immense unmet need for targeted therapies such as amivantamab, in the absence of effective standard of care (SoC) treatments. This is also acknowledged by the NICE Committee in the ACD (page 5): *"The committee concluded that there is an unmet need for more effective treatment options that specifically target the exon 20 insertion mutations."*

Further, Janssen considers that there are a number of benefits of amivantamab that are not captured in the cost per quality-adjusted life year (QALY) calculations that should be taken into account for committee decision making:

- Amivantamab provides benefits aligned with patient preferences
- The value of hope associated with a treatment that improves survival outcomes
- Patients place more value on later line treatments such as amivantamab given the effects of stigmatisation within NSCLC in delaying treatment seeking behaviours and thus NIE should consider the stigma as a social value judgement issue.
- Amivantamab would alleviate both patient and caregiver burden.

Janssen have provided a response which focusses on areas of uncertainty that were identified by the AC, with a particular focus on the provision of information (such as the completion of the DataSAT Checklist) to further reassure the AC that the real-world evidence (RWE) analyses informing the efficacy of UK SoC in the submission are robust, reliable and fit for purpose.

Overall, this response covers the following points:

- The reporting of the real-world evidence for the comparator arm
- The stigma associated with EGFR Exon20ins NSCLC
- The most appropriate approach for amivantamab time on treatment
- The addition of a scenario exploring the impact of diagnostic testing costs
- Revised base case cost-effectiveness analysis and revised PAS
- Benefits not captured within the cost per QALY framework
- Factual inaccuracies
- Confidentiality highlighting errors

	As indicated in the bullet points above, a revised PAS has been included as part of this response, representing a [redacted] discount on the list price of amivantamab.
Section 1	**The reporting of the real-world evidence for the comparator arm** Page 9 of the ACD states: *"the committee considered that the company had not provided enough information on data provenance, data accuracy and data suitability, and had not explored the effect of missing data. The committee concluded that the way the company had chosen and used real-world evidence was associated with several areas of uncertainty."* As per the original submission, and as noted by the AC, due to the single arm nature of the CHRYSALIS trial and the rarity of EGFR Exon20ins-mutated NSCLC, RWE is the most appropriate available source of comparator efficacy evidence, and demonstrates that amivantamab is associated with a consistent and statistically significant treatment benefit when compared to current SoC treatments across all endpoints. However, to address the uncertainty highlighted by the evidence review group (ERG) and AC in the ACD, Janssen have provided additional information below regarding the use of RWE within the submission. • *"The committee noted that the company could have used well-validated real-world evidence checklists and reporting tools (such as the RECORD-PE checklist or the STaRT-RWE template)."* Janssen have now completed the DataSAT checklist, as recommended by the NICE RWE framework.[1] This is provided in Appendix 2 of this response. • *"The company could have done a sensitivity analysis using a multiple imputation approach to assess the impact of missing data."* Janssen have now conducted sensitivity analyses assessing the impact of missing data on the indirect analyses informing the comparison of amivantamab versus UK SoC utilising US RWE. The following analyses have been conducted: • Amivantamab versus pooled US RWE with imputation for missing values • Amivantamab versus pooled US RWE with imputation for missing values and with TKIs excluded • Amivantamab versus Flatiron with imputation for missing values • Amivantamab versus Flatiron with imputation for missing values and with tyrosine kinase inhibitors (TKIs) excluded ConcertAI did not have any missing values and therefore a multiple imputation approach was not required to be investigated in a sensitivity analysis. Whilst COTA did have some missing values (for number of metastatic locations), adjusting for all covariates including this covariate led to a large degree of imbalance; therefore, only covariates up to and including Eastern Cooperative Oncology Group performance status (ECOG PS) were adjusted for. Therefore, results with imputation do not apply to COTA. The results of these analyses are presented in Table 13 of Appendix 3 below. Analyses of amivantamab versus each US source individually with and without the exclusion of TKIs are also presented in Appendix 3 without consideration of the imputation of missing values, in line with the base case approach from the Company Submission. Overall, the results demonstrate consistency across endpoints and data sources irrespective of the application of imputation and/or the inclusion/exclusion of TKIs.

- *"It could also have reduced uncertainty by providing further detail on how it chose data sources and assessed their suitability. In particular, for each of the 3 US real-world evidence sources in the company base case, further information to reduce uncertainty could have included:*
  - *a description of each data source and the number of people included"*

Information on the eligibility criteria for each US data source can be found in Table 1 below.

Table 1: Eligibility criteria for each US data source

ConcertAI	COTA	Flatiron
Inclusion criteria:		
• Aged ≥18 years at the time of Stage IIIB, IIIC, or IV NSCLC diagnosis • Pathology consistent with NSCLC • Stage IIIB, IIIC, or IV NSCLC, either at the time of their initial NSCLC diagnosis or after development of recurrent or progressive disease • Documented EGFR Exon20ins result at any time after their initial NSCLC diagnosis	• NSCLC • Confirmed EGFR Exon20ins	• ICD code for lung cancer (ICD-9-CM • 162.x, ICD-10 C34x, C39.9) • ≥2 documented clinical visits in the Flatiron EHR on or after 1/1/2011 • Abstractor-confirmed pathology consistent • with NSCLC • Diagnosed with Stage IIIB, IIIC, IVA, or IVB NSCLC on or after 1/1/2011 or early stage NSCLC that later developed into abstractor-confirmed, recurrent or progressive disease on or after 1/1/2011 • Received ≥1 line of therapy in the advanced NSCLC setting • Positive EGFR Exon20ins result at any time
Exclusion criteria:		
• Insufficient EHR data	• Multiple concurrent primary cancer diagnoses, or not actively treated at 1 of the 5 sites, or had insufficient EHR data	• No records of visits or medication orders in the EHR in the 90 days after their abstracted advanced NSCLC diagnosis date

Abbreviations: CM: clinically modified; EGFR: epidermal growth factor receptor; EHR: electronic health record; Exon20ins: exon 20 insertion mutations; ICD: International Statistical Classification of Diseases and Related Health Problems; LOT: line(s) of therapy; NSCLC: non-small cell lung cancer.

The methodology by which the lines of treatment (LOTs) ultimately used in the adjusted analysis were derived is presented in Table 1 of Minchom *et al.* (2022; see Table 6,

	Appendix 1).[2] Additionally, in the analysis informing this submission specifically, exclusion of LOTs for patients who were not diagnosed with NSCLC with EGFR Exon20ins at the time of LOT start was conducted, leading to [redacted] patients representing [redacted] LOTs. o *"a description of the provenance of the data source"* Further information on data provenance can be found in the DataSAT checklist provided in Appendix 2. o *"further information on key study variables and outcomes, including details on data availability and completeness, how they were measured and derived from the data, whether any linkage to external data sources was included and an assessment of accuracy"* Further information on key study variables and outcomes can be found in the DataSAT checklist provided in Appendix 2. o *"a description of the missing data and the number of people excluded from the analyses at each step of filtering (for example, how many people were filtered because of each eligibility criterion or because of missing data on key confounding variables)"* As described above, details regarding patient disposition from the US RWE sources can be found in Table 1 of Minchom *et al.* (2022; see Table 6, Appendix 1), including the number of LOTs excluded at each stage of the analysis for both the pooled US data set and each contributing source individually.[2] Additionally, a further criteria was applied for the analysis informing the Company Submission: exclusion of LOTs for patients who were not diagnosed with NSCLC with EGFR Exon20ins at the time of LOT start, meaning that [redacted] LOTs were included in the final analysis set of interest. Missing data for baseline demographics and clinical characteristics for the US RWE sources (pooled and by source) can be found in Table 2 of Minchom *et al.* (2022; see Table 7, Appendix 1) for Race, smoking history and ECOG performance status.[2] Race and smoking history were not included as covariates in the adjusted analyses (reasons for this are described in Table 59 of the Company Submission appendices). Additionally, data were missing from Flatiron ([redacted]) and COTA ([redacted]) for the covariate of 'number of metastatic locations'. Sensitivity analyses utilising a multiple imputation approach to account for these missing data are presented in Table 13. o *"the time period when the information was collected for each variable in the real-world evidence, defined in relation to the treatment start date."* Further information on the time frame of data collection can be found in the DataSAT checklist provided in Appendix 2. • *"The committee also noted that a full study protocol for each of the real-world evidence sources according to the NICE real-world evidence framework requirements should be provided."* The study protocol for the RWE study comparing CHRYSALIS to the three US data sources is included in the reference pack.[3]
Section 2	**The stigma associated with NSCLC with EGFR Exon20ins**

	Janssen would like to reiterate that EGFR-positive NSCLC (of which NSCLC with EGFR Exon20ins is a part) is associated with significant stigma as a result of being associated with smoking behaviours, despite the fact that, relative to other lung cancers, this population has a larger proportion of patients who are never-smokers (see Table 3 of Document B).[4-6] Some patients report feeling uncomfortable communicating their symptoms, which can lead to delays in presentation, diagnosis and treatment (or low uptake of treatment).[7] In particular, the patient/caregiver survey reported in Document B of the Company Submission showed that 42% of patients feel that some healthcare professionals (HCPs) are less sympathetic to people with lung cancer than other cancers, while 55% felt that HCPs assume they are or used to be a smoker. As a result, 15% of patients reported delaying seeing a HCP and/or delayed taking treatment as a result of concern about other people's attitudes to lung cancer.[5] Patients with advanced-stage NSCLC also have been observed to be less likely to experience guideline-concordant care that patients with other cancers due to the effects of stigmatisation.[8] Overall, stigmatisation therefore contributes to delayed diagnosis and treatment. Consequently, it is important for effective treatment options to be available at advanced stages of disease, placing a higher value on later line therapies. This value has not been captured in the cost-effectiveness model underpinning this submission, and should therefore be taken into account for Committee decision making as a social value judgement issue. In NICE's social value judgements, the following is stated relating to stigma in the context of avoiding discrimination and promoting equality: *"NICE is aware that stigma may affect people's behaviour in a way that changes the effectiveness of an intervention and that the relief of stigma may not always be captured by routine quality of life assessments."* Linked to the statement on stigmatisation influencing the effectiveness of an intervention, research conducted by the British Lung Cancer Foundation showed that for some people living with lung disease, feeling socially isolated and stigmatised exacerbates the negative impacts of their symptoms.[9] This was further demonstrated by the market research funded by Janssen in a total of 40 people living with EGFR positive (EGFR+) lung cancer and four of those with EGFR Exon20ins. The quantitative research in EGFR+ lung cancer showed that more than a third of the patients who took part in the survey reported that negative attitudes towards their lung cancer have made it harder for them to cope emotionally with their condition. In one study by Brown *et al.* (2014), lung cancer stigma was positively correlated with anxiety and depression and negatively correlated with quality of life (QoL) and stigma was considered to explain (to a small but significant degree) variance in QoL, and that this was the case both in smokers and never-smokers. This study also suggested that decreased QoL associated with stigma may be a result of both physical and emotional responses to stigma, such as increased symptom burden and negative self-concept, leading to decreases in QoL as observed by lower scores on assessed physical, psychological and social well-being subscales.[10] On the point regarding relief of stigma, the relief of stigma that amivantamab may induce due to the clinical benefits of this intervention compared to UK SoC (which may occur if patients experience better quality of life and are therefore less obviously suffering from a disease that may be perceived by society as self-inflicted), would not be captured in the QoL measures feeding into the economic model for this submission, but are an important aspect within this patient population given the prevalence of stigmatisation in patients with advanced NSCLC with EGFR Exon20ins.
Section 3	**The most appropriate approach for amivantamab time on treatment**

	Janssen maintain that the most appropriate approach to model time on treatment for amivantamab is via treat-to-progression as per marketing authorisation. Janssen wish to emphasise that UK-based clinicians stated that patients would discontinue treatment with amivantamab upon experiencing a progression event, and thus we maintain that the assumption that time to treatment discontinuation (TTD) is equal to progression-free survival (PFS) is appropriate. In addition, it is important to note that patients in clinical trials are monitored more closely than in the real world and as such, progression in CHRYSALIS would have been detected earlier than it would in real-world clinical practice. Progression is not a hard stop, rather it evolves at the cellular level before impacting patient health-related quality of life (HRQoL). Therefore, the use of early detected progression to inform HRQoL may underestimate the benefit of amivantamab. However, in acknowledgement of the concerns of the ERG and AC regarding this assumption, a scenario based on the revised base case exploring the Gompertz curve choice for amivantamab TTD is also presented as a scenario analysis. The rationale for this selection, rather than the use of the Exponential, is described below. In the ACD, the AC state that *'It is appropriate to base time on treatment on CHRYSALIS time to treatment discontinuation data, extrapolated using the exponential curve'*. Whilst the company understand that the ERG and AC prefer the use of TTD data from CHRYSALIS, Janssen disagree with this statement. If the use of TTD is to be taken forward, then the Exponential curve is not the most appropriate curve choice to select. As previously described by the company, although the Exponential curve has the best statistical fit, the Gompertz or Weibull curves are more appropriate selections as statistical fit is not the only consideration of relevance when selecting the most appropriate curve. Additionally, when considering the TTD extrapolation for amivantamab (see Figure 1), statistical fit might not be the most reliable measure, because the fit at the start of the Kaplan-Meier is very similar between curves and only towards the end of the timeframe does it diverge. At later timepoints, there are fewer patients at risk so the statistical fit to the Kaplan-Meier is less relevant.

Figure 1: Amivantamab TTD extrapolations and Kaplan-Meier data

Abbreviations: TTD: time to treatment discontinuation; KM: Kaplan-Meier.

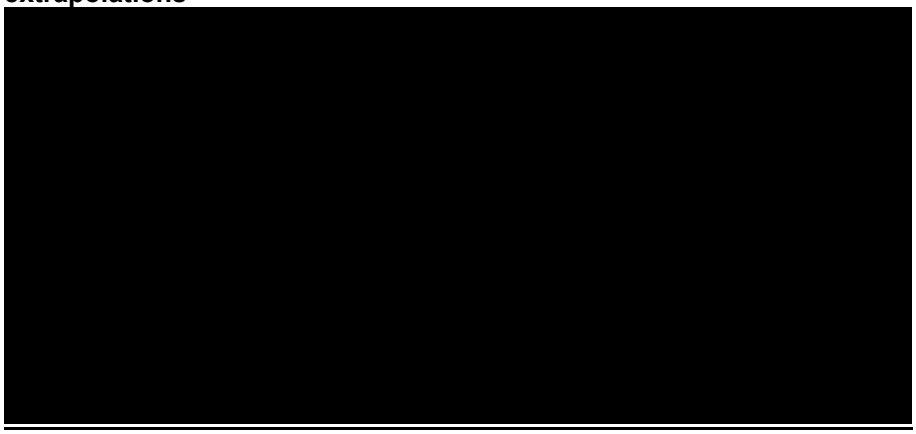
Further, as previously described, the Gompertz is most aligned with smoothed hazard curve for TTD (see Figure 2 below). The Exponential curve assumes constant hazards over time, which is not aligned with the hazards demonstrated for amivantamab TTD.

The relationship to PFS can also be considered in selecting an appropriate curve for TTD. When assessing this relationship, for the Exponential curve, patients remain on treatment beyond progression, and the difference between TTD and PFS is particularly prominent towards the tail of the extrapolations. For both Gompertz and Weibull, patients remain on treatment beyond progression but the difference is not as prominent and is more aligned throughout with a narrowing at the tail (see Figure 3).

Figure 2: CHRYSALIS TTD – smooth and unsmoothed

Abbreviations: TTD: time to treatment discontinuation.

Figure 3: Relationship between TTD and PFS with the Exponential and Gompertz extrapolations



Abbreviations: KM: Kaplan-Meier; OS: overall survival; PFS: progression-free survival; SoC: standard-of-care; TTD: time to treatment discontinuation.

The results of a scenario analysis implementing a Gompertz selection for amivantamab TTD is presented in Table 2 below.

Table 2: Deterministic scenario analysis results – amivantamab ToT=TTD (Gompertz)

	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)

	<table><tr><td>**Base case**</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£27,766</td></tr><tr><td>Amivantamab ToT=TTD (Gompertz)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£37,091</td></tr></table> **Abbreviations**: ICER: incremental cost-effectiveness ratio; LY: life years; Incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years.
Section 4	**The addition of a scenario exploring the impact of diagnostic testing costs** As requested by the AC, Janssen have conducted a scenario analysis exploring including the cost of testing for EGFR Exon20ins in NSCLC at £550 per patient with NSCLC with EGFR Exon20ins. The results of this scenario analysis are presented in Table 3 below based on the updated base case (see Section 5) and demonstrate that the addition of the testing costs marginally increases the with-PAS ICER from [redacted]. **Table 3: Deterministic scenario analysis results – inclusion of diagnostic testing costs** <table><tr><th></th><th colspan="3">LIST PRICE</th><th colspan="3">WITH PAS</th></tr><tr><th></th><th>Incr. costs (£)</th><th>Incr. QALYs</th><th>ICER (£/QALY)</th><th>Incr. costs (£)</th><th>Incr. QALYs</th><th>ICER (£/QALY)</th></tr><tr><td>**Base case**</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£27,766</td></tr><tr><td>Inclusion of testing costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£28,733</td></tr></table> **Abbreviations:** ICER: incremental cost-effectiveness ratio; LY: life years; Incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years.
Section 5	**Revised base case cost-effectiveness analysis and revised PAS** Janssen present a revised company base case, accommodating the following assumptions as preferred by the AC: • excluding EGFR TKIs from the blended comparator arm • using the inverse probability weighting method for the indirect treatment comparison • using utility values from TA713 • using parametric modelling to represent survival in the blended comparator arm • excluding treatment waning This base case assumes that time on treatment for amivantamab equals PFS for the reasons described in Section 3. A scenario analysis considering TTD data for amivantamab (Gompertz) is presented in Table 2 above. The revised base-case deterministic and probabilistic cost-effectiveness analyses are presented in Table 4 and Table 5 below. As mentioned in the executive summary, the PAS for amivantamab has been updated. 'With PAS' results incorporate this new discount.

Table 4. Updated base case results at amivantamab PAS price (deterministic)

	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
UK SoC	[redacted]	[redacted]	1.35	-	-	-	-
AMI	[redacted]	[redacted]	2.27	[redacted]	[redacted]	0.92	£27,766

Abbreviations: AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

Table 5. Updated base case results at amivantamab PAS price (probabilistic)

	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
UK SoC	[redacted]	[redacted]	1.36	-	-	-	-
AMI	[redacted]	[redacted]	2.28	[redacted]	[redacted]	0.92	£28,909

Abbreviations: AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

Benefits not captured within the cost per QALY framework

As described in the Executive Summary, there are a number of benefits of amivantamab which are not explicitly captured in the QALY calculation, which, if included, would improve the cost-effectiveness of amivantamab further.

The impact of stigma on delayed diagnosis and treatment is described in detail in Section 2; however, additional considerations beyond this are elaborated upon here.

Providing benefits which are aligned to patient and caregiver preferences are not considered in the QALY framework. The extended period progression-free or alive associated with amivantamab versus UK SoC may reduce the anxiety associated with progression or death observed in both patients and carers. Prolonged time progression-free may also lead to improvement in aspects of daily life most valued by patients, such as being able to undertake daily activities, maintaining independence and 'feeling normal' (as described in Section B.1.3.1 of Document B), the value of which is not intrinsically captured in the QALY framework. Further, patients become frustrated when they are told that although they have an EGFR positive mutation, that their particular mutation cannot be treated with EGFR TKIs. Therefore, the value of hope associated with receiving a targeted treatment for NSCLC with EGFR Exon20ins is incredibly high and is also not intrinsically captured. In addition, patients with NSCLC with EGFR Exon20ins have a poorer prognosis than other patients with common EGFR mutations where there is a larger degree of treatment choice with a proven benefit.[6] Therefore, this also supports that there is additional value in amivantamab being available to patients as an additional treatment option for use by oncologists beyond the limited treatment options for these patients compared with those for patients with EGFR common mutations.

In-depth interviews with patients with NSCLC with EGFR Exon20ins have revealed that patients anticipate negative views from others and are reluctant to share their diagnosis with their employers and wider society for fear of being seen as responsible for their illness. Many patients have experienced unfair treatment due to their diagnosis, with 55% having experienced stereotypes about people who have lung cancer and 28% have experienced prejudice towards people with lung cancer. Given the benefits that amivantamab may bring as compared to the current UK SoC, this may lead to alleviation

Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 16 September 2022. Please submit via NICE Docs.

	of stigma, which would not be captured in generic QoL measures and therefore in QALY calculations.[5] Additionally, for those living with NSCLC with EGFR Exon20ins, anticipated stigma can impact their ability to work as they do not want to be judged or excluded in the work setting. Some patients that were interviewed spent so much time worrying about work, the opinions of their colleagues and their financial situation that this ultimately contributed to feeling they needed to stop working due to the emotional strain. This was further shown in the quantitative survey conducted in EGFR+ patients with 35% worrying or experiencing discrimination in the workplace.[5] The inextricable link between stigma and discrimination in the workplace in those that were sampled demonstrates that stigma may have productivity implications for some patients. Any benefits in terms of the alleviation of this indirect economic burden would not be captured within the economic model.
Section 6	**Factual inaccuracies** • Page 9 of the ACD states *"In contrast, the NCRAS evidence only provided data on time to next treatment and overall response rate."* Janssen would like to clarify that the NCRAS (Public Health England [PHE]) data source only provided data on time to next treatment and **overall survival**. Overall response rate data were not available from the NCRAS data set. • Janssen would like to clarify a misunderstanding around why updated efficacy analyses from the n=153 population could not be provided; as noted on Page 7 of the ACD. The AC noted that Janssen did not provide a reason for why efficacy analyses for this population were not presented. The n=153 population included all patients with NSCLC with EGFR Exon20ins who received prior chemotherapy at the recommended Phase 2 dose (RP2D) prior to the 30 March 2021 data cut-off. However, the n=114 efficacy population included all patients with NSCLC with EGFR Exon20ins who received the RP2D prior to 04 June 2020 data cut-off with **≥3 disease assessments** as of the 08 October 2020 data cut-off. This difference in the populations means that efficacy data are not available for the larger n=153 population as not all patients in the safety population had received **≥3 disease assessments** to be considered for an efficacy analysis set.
Section 7	**Confidentiality highlighting errors** • Page 12 of the ACD states the number of patients that EuroQoL-5 dimensions-5 levels (EQ-5D-5L) data were collected within the CHRYSALIS trial without academic in confidence highlighting. This should be amended as follows: *"The company explained that EQ-5D-5L data from the CHRYSALIS trial was collected for only* [redacted] *people, and only for the progression-free survival state."*

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence

information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

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Appendix 1: Supplementary information from Minchom *et al.* (2022)

Table 6: Patient disposition after applying key CHRYSALIS inclusion criteria and after de-duplication from Minchom *et al.* (2022)

	Pooled		Flatiron		ConcertAI		COTA	
	n	Reduction	n	Reduction	n	reduction	n	Reduction
Received from vendor	391	-	200	-	99	-	92	-
Advanced NSCLC with EGFR Exon20ins	371	5.1%	200	0.0%	96	3.0%	75	18.5%
≥18 years at advanced NSCLC diagnosis	371	0.0%	200	0.0%	96	0.0%	75	0.0%
Platinum-based chemotherapy after metastatic diagnosis or in 12 months prior	282	24.0%	144	28.0%	75	21.9%	63	16.0%
≥1 LOT after platinum-based chemotherapy	193	31.6%	97	32.6%	54	28.0%	42	33.3%
ECOG PS score of 0 or 1 (or missing) at start of qualifying therapy	180	6.7%	88	9.3%	50	7.4%	42	0.0%
No record of other malignancy in 3 years before start of qualifying therapy	174	3.3%	84	4.5%	48	4.0%	42	0.0%
After de-duplication	125[a]	28.2%	84	0.0%	35	27.1%	39	7.1%

[a]Excludes LOT from patients with missing ECOG PS scores.
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; Exon20ins: exon 20 insertion mutations; LOT: line of therapy; NSCLC: non-small cell lung cancer.
Source: Minchom *et al.* (2022).[2]

Table 7: Baseline demographics and clinical characteristics for all qualifying LOT for each patient (without weighting).

	Pooled[a]	Flatiron	ConcertAI	COTA
n (LOT)	125 (227)	84 (168)	48 (102)	42 (98)

Age, median [min; max]	62.0 [31.0; 84.0]	65.0 [40.0; 82.0]	61.5 [36.0; 84.0]	61.0 [31.0; 78.0]
Sex, n (%)				
Female	137 (60.4)	90 (53.6)	64 (62.7)	59 (60.2)
Male	90 (39.6)	78 (46.4)	38 (37.3)	39 (39.8)
Race, n (%)				
Asian	27 (13.0)	20 (12.8)	0 (0.0)	7 (7.5)
Black or African American	11 (5.3)	5 (3.2)	11 (12.2)	8 (8.5)
White	140 (67.3)	100 (64.1)	62 (68.9)	75 (79.8)
Other	30 (14.4)	31 (19.9)	17 (18.9)	4 (4.26)
Missing	19 (8.4)	40 (23.8)	12 (11.8)	4 (4.1)
Smoking history, n (%)				
No	133 (58.8)	89 (53.0)	62 (62.0)	53 (54.1)
Yes	93 (41.2)	79 (47.0)	38 (38.0)	45 (45.9)
Missing	1 (0.44)	0 (0.0)	2 (1.96)	0 (0.0)
ECOG PS score, n (%)				
0	69 (30.4)	35 (33.3)	35 (43.2)	6 (7.9)
1	158 (69.6)	70 (66.7)	46 (56.8)	70 (92.1)
2[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	63 (37.5)	21 (20.6)	22 (22.4)
Brain metastasis at baseline, n (%)				
No	137 (60.4)	108 (64.3)	64 (62.7)	57 (58.2)
Yes	90 (39.6)	60 (35.7)	38 (37.3)	41 (41.8)
Prior lines in metastatic setting,[c] n (%)				
0–1	100 (44.1)	77 (45.8)	47 (46.1)	38 (38.8)
2	63 (27.8)	42 (25.0)	25 (24.5)	32 (32.7)
3+	64 (28.2)	49 (29.2)	30 (29.4)	28 (28.6)
Time from advanced diagnosis to LOT (months), median [min; max]	14.8 [0.23; 85.6]	14.6 [0.39; 54.5]	13.5 [0.10; 55.2]	15.3 [0.69; 85.6]

[a]After de-duplication and exclusion of patient LOT with missing ECOG PS scores. [b]One enrolled patient was reclassified as having an ECOG PS score 2 rather than 1. [c]Does not include neo-adjuvant/adjuvant platinum-based chemotherapy (or any other therapy) before date of metastatic NSCLC diagnosis.
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; LOT: line of therapy.
Source: Minchom *et al.* (2022).[2]

Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

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Appendix 2: DataSAT RWE checklist

Table 8: Data provenance

Item	Information	Response		
DATA SOURCES	*For each contributing data source provide the name, version and date of data cut. Provide links to their websites, if available.*	Flatiron Health Spotlight: https://flatiron.com/real-world-evidence/ Version: 2 Data cut-off: April 30th 2020	ConcertAI: https://www.concertai.com/ Version: 2 Data cut-off: September 20th 2021	COTA: https://cotahealthcare.com/ Version: 2 Data cut-off: January 5th 2021
DATA LINKAGE AND DATA POOLING	*Report which datasets were linked, how these were linked, and performance characteristics of the linkage. Note whether linkage was done by a third party (such as NHS Digital).* *Clearly describe which data sources were pooled.*	Data from the three US data sets (Flatiron Health Spotlight, ConcertAI and COTA) were pooled to maximise sample size. Direct access to IPD from the data sources allowed for pooling of data. Some patients were captured multiple times due to overlap of the data sources. As such, patients in the Flatiron database were removed from ConcertAI and COTA databases, and patients in the ConcertAI database were removed from the COTA database. Details of de-duplication can be found in Table 1 of Minchom *et al.* (2022).[2] There was no linkage across the datasets; only de-duplication was performed. De-duplication using a tokenisation procedure allowed for the US statute, Health Insurance Portability and Accountability Act of 1996-compliant identification of duplicate patients across the three real-world datasets.[2]		
TYPE OF DATA SOURCE	*Describe the types of data source (for example, electronic health record, registry, audit, survey).*	Flatiron Health aggregates EHR data from cancer clinics in the US, mostly in the community oncology setting using OncoEMR	ConcertAI aggregates EHR data from cancer clinics, mostly in the community oncology setting. The ConcertAI dataset includes both data derived from	COTA abstracts data from EHR of healthcare provider sites, representing diverse treatment settings

		software. This Spotlight dataset includes both data derived from structured fields in the EHR (e.g., laboratory values and prescribed drugs) and additional data elements abstracted from physicians' notes and other documents (e.g., biomarker reports).	structured fields in the EHR (e.g., laboratory values and prescribed drugs) and data abstracted from physicians' notes and other documents (e.g., biomarker reports).	including academic, for-profit, community sites, and hospital systems.
PURPOSE OF DATA COLLECTION	*Describe the main purpose of data collection (for example, clinical care, reimbursement, device safety, research study).*	Janssen-initiated research study to inform reimbursement submissions for amivantamab.		
DATA COLLECTION	*Describe the main types of data collected (for example, clinical diagnoses, prescriptions, procedures, patient experience data), how data was recorded (for example, clinical coding systems, free text, remote monitoring, survey response), and who collects the data (for example, healthcare professional, self-reported, digital health technology). If*	**Main types of data collected** Data were collected on patient baseline characteristics, treatments and clinical outcomes (ORR, PFS, OS and TTNT). Data are not available on treatment adherence. **How data were recorded** As described above, data were collected from structured fields in the EHR, or were abstracted by trained abstractors from documents scanned into EHR.		

	the nature of data collection has changed during the data period (for instance, change in coding system or practices, data capture systems) describe the changes clearly. Any differences between data providers in how and what data were collected and its quality should be described. *If additional data collection was done for a research study please describe, including how the validity and consistency of data collection was assured (for example, training).*	**Differences between data providers in how and what data were collected and its quality** COTA relies solely on abstractors to create all data fields that are delivered to the sponsor, whereas ConcertAI and Flatiron use abstractors to create some data fields and pass on other data fields directly from structured fields in the EHR. All providers use quality control processes (e.g., audits) to ensure quality of data. The sponsor further carried out quality checks (e.g., ensuring that all patients had a qualifying EGFR Exon20ins), which led to some corrections of data by the providers. **If additional data collection was done for a research study please describe, including how the validity and consistency of data collection was assured** Baseline characteristics for the CHRYSALIS trial and US RWE data sources were similar, with UK clinical experts confirming the high degree of alignment between the data sources.[11] The endpoints in both the CHRYSALIS trial and RWE data sources are defined as below: • ORR was defined as the proportion of all patients who achieved a confirmed partial response or better. For the RWE data sources, this was measured amongst those with at least one non-missing record of response only. • PFS was defined as the interval between the index date and the date of disease progression or death (patients initiating subsequent anticancer therapy in the absence of progressive disease were censored on the date of the last disease

		assessment before the start of subsequent therapy in CHRYSALIS, and at the start of subsequent therapy for real-world data sources). • OS was defined as the time between index date and date of death (or censoring). • TTNT was defined as the interval between index date and initiation of subsequent systemic anti-cancer therapy or death (for patients without a record of subsequent anti-cancer therapy, the interval was censored at the date of last contact with the patient). For patients in the CHRYSALIS trial, response and progression evaluations were based on RECIST v1.1 criteria. For patients in real-world data sources, response and progression were defined as clinically relevant response or progression in the opinion of the treating physician; it was generally not possible to check whether RECIST v1.1 criteria were applied. ORR and PFS in CHRYSALIS were assessed by both investigator (INV) and Independent Reviewing Committee (IRC). For patients in the CHRYSALIS trial, the index date was the date of the first amivantamab dose. For patients from the real-world data sources, the index date was the start of any line of therapy for which inclusion and exclusion criteria were met upon initiation.	
CARE SETTING	*State the setting of care for each dataset used (for example, primary care, secondary care, specialist health centres, social services, home use [for wearable devices, or self-*	Patients were from US cancer clinics, primarily in the community oncology setting.	79% of these patients were treated at academic medical centres and 21% were treated in the community oncology setting.

<table>
<tr><td></td><td>reported data on apps or websites]).</td><td colspan="2"></td></tr>
<tr><td>GEOGRAPHICAL SETTING</td><td>State the geographical coverage of the data sources.</td><td>US

The geographic breakdown of the Flatiron aNSCLC Core Registry is approximately 20% Northeast, 17% Midwest, 45% South, 17% West and 1% Puerto Rico.</td><td>US

Further breakdown is not available due to privacy concerns.</td></tr>
<tr><td>POPULATION COVERAGE</td><td>State how much of the target population is represented by the dataset (for example, population representativeness or patient accrual).</td><td colspan="2">The baseline characteristics of all data sources (CHRYSALIS, US pooled [Flatiron, ConcertAI and COTA] and PHE RWE data sources) were validated as representative of the UK patient population by UK clinical experts during an advisory board.[11] In addition, the characteristics for each US source individually are presented in Table 9 below, alongside those from the CHRYSALIS trial and show broad alignment between each source, except for the number of metastatic locations, which is variable between sources.

Table 9: Baseline characteristics from CHRYSALIS and each US data source
<table>
<tr><th></th><th>Amivantamab (N=114)</th><th>Flatiron (N=93)</th><th>ConcertAI (N=51)</th><th>COTA (N=62)</th></tr>
<tr><td colspan="5">Prior lines of treatment</td></tr>
<tr><td>1</td><td></td><td>[redacted]</td><td></td><td>[redacted]</td></tr>
<tr><td>2</td><td></td><td>[redacted]</td><td></td><td>[redacted]</td></tr>
<tr><td>3</td><td></td><td>[redacted]</td><td></td><td>[redacted]</td></tr>
<tr><td>4+</td><td></td><td>[redacted]</td><td></td><td>[redacted]</td></tr>
<tr><td colspan="5">Brain metastasis</td></tr>
<tr><td>No</td><td></td><td>[redacted]</td><td></td><td>[redacted]</td></tr>
<tr><td>Yes</td><td></td><td>[redacted]</td><td></td><td>[redacted]</td></tr>
</table></td></tr>
</table>

		Age <60 [redacted] 60–70 [redacted] ≥70 [redacted] **ECOG PS** 0 [redacted] 1 [redacted] **Number of metastatic locations** 1 [redacted] 2 [redacted] 3 [redacted] 4+ [redacted] Missing [redacted] **Haemoglobin** Normal/High [redacted] Low [redacted] **Gender** Male [redacted] Female [redacted] **Cancer stage at initial diagnosis** I [redacted] II [redacted] IIIA [redacted] IIIB/IV [redacted] **Abbreviations:** ECOG PS: Eastern Cooperative Oncology Group Performance Status.
TIME PERIOD OF DATA	*State the time period covered by the data.*	15 December 2009–16 October 2020

DATA PREPARATION	*Provide details of whether raw data were accessed for analysis, or whether the data owner had undertaken any data preparation steps such as cleansing or transformation. Mention whether centralised transformation to a common data model was undertaken. Include links to any relevant information including common data model type and version number and details of mapping.* *Full details of data preparation specific to addressing the research question is covered in the section on reporting on data curation.*	Some data cleaning and preparations were carried out for following purpose: • Windowing ECOG values • Cleaning unacceptable response values	Some data cleaning and preparations were carried out for following purpose: • Defining lines of therapy, to achieve consistency with the Flatiron dataset • Windowing ECOG values • Cleaning unacceptable response values	Some data cleaning and preparations were carried out for following purpose: • Defining lines of therapy, to achieve consistency with the Flatiron dataset • Converting from KPS to ECOG and windowing ECOG values • Cleaning unacceptable response values
DATA GOVERNANCE	*Provide the details of the data controller and funding for each source. Describe the information governance processes for data access and use.*	The RWE study was funded by Janssen.		

DATA SPECIFICATION	*Note whether a data specification document is available. This may include a data model, data dictionary, or both.*	No additional information available.	No additional information available.	No additional information available.
DATA MANAGEMENT PLAN AND QUALITY ASSURANCE METHODS	*Note whether a data management plan, documentation of source quality assurance methods is available with links to relevant documents.*	Flatiron maintains policies and procedures for QA: Flatiron data abstractors are qualified by training and experience. Training and experience are assessed through external experience (such as direct experience with oncology and/or research) as well as Flatiron-specific training and experience (e.g., training on procedures, Flatiron systems). Operating procedures and documented best practice guidelines are used to promote quality and consistency. Quality monitoring governs the abstraction process.	Data QC was comprised of both human review and programmatic validation. Manual review involved the review of curated records by the Project Curation Management Team for consistency, completeness, accuracy and compliance with eligibility criteria and curation instructions. Where review uncovered data issues with these criteria, queries were issued to the curation team for resolution. Manual review was conducted on two levels: • A subset of records were reviewed in their entirety by Project Curation Management	COTA assesses data quality across key milestones in the data pipeline to ensure the generation of high quality real-world data that can be transformed into fit-for-purpose datasets. Key QA processes are described in more detail below: **Abstractor Training and Testing:** COTA abstractors are trained using standardised, version-controlled instructions. Abstractors are required to achieve an acceptable accuracy rate on test records against a gold standard prior to entering production. If an abstractor's initial records in production do not maintain the minimal accuracy threshold, the

		Indication-specific QA includes the following: • A risk-based sample of data elements are duplicate abstracted (e.g., data for the same patient is abstracted by two different abstractors) to confirm agreement and ensure consistency of variable collection. • Medical outliers or edge cases are escalated via a "Review Panel" for adjudication by Flatiron's Abstraction team leads, QA specialists, and/ or medical oncologists.	• In addition, certain key variables, such as those related to inclusion/exclusion criteria, were reviewed for 100% of records. Programmatic validation included testing curated data for logical consistency and flagging results for review and correction by the curation team. For example, this includes ensured ordinality of related date variables, testing for fill rates and/or missingness, and other edit checks. Programmatic checks conducted on each variable were specified in the variable descriptions and are executed against 100% of records.	abstractor is removed from production and provided with additional training. **Programmatic Data Entry Validation:** COTA's abstraction platform has built-in features to flag data that requires review for plausibility (e.g., future dates, events after death, extreme values, and many others). **Escalation Process:** COTA has an escalation process in which abstractors can escalate scenarios that require insight or reconciliation by a senior QA team member (including COTA medical oncologists, if necessary). Escalated scenarios include conflicting documentation in the EHR, challenging or unique clinical scenarios, project-specific qualification, and others.

		Additionally, feedback is provided to abstractors.		**Record Audits:** approximately 10% of records contributing to active deliverables undergo complete review by QA staff. In this process, the entire record is audited for accuracy and completeness. In 2020, COTA implemented double-blind abstraction and inter-rater reliability testing as a measure of abstractor agreement. **Deliverable-specific Programmatic Checks:** COTA conducts programmatic assessments of data quality on each dataset deliverable. Assessments include missingness, distribution, and plausibility of values. Output from the programmatic checks is reviewed cross-functionally and sent back for clinical abstractor investigation and adjudication, if needed. These checks include the validation of

				any project-specific inclusion/exclusion criteria and summary statistics to support deliverable review. **Cross-functional deliverable review:** each COTA project has a cross-functional working team that conducts a review of the dataset prior to delivery. This review focuses on assessing completeness.
OTHER DOCUMENTS	*Note whether any other documentation is available. Provide hyperlinks or citations to key publications, if available.* *If the dataset is available from the HDRUK innovation gateway, provide the hyperlink to its profile on the HDRUK website.*	The following documents are available and are included in the reference pack for this ACD response document: • Study protocol for amivantamab versus US RWE sources[3] • Statistical analysis plan for amivantamab versus US RWE sources[12] • ConcertAI data manual • COTA data manual • Flatiron analytic guide		

Table 10: Data quality

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
WHAT TYPE OF VARIABLE (FOR EXAMPLE, POPULATION ELIGIBILITY, OUTCOME)	*Define the target concept (for example, myocardial infarction [MI])*	*Define operational definition. For example, MI defined by an ICD-10 code of I21 in the primary diagnosis position*	*Choose: accuracy or completeness*	*Describe how quality was assessed. Provide reference to previous validation studies if applicable.*	*Provide quantitative assessment of quality if available. For example, 'positive predictive value 85% (75% to 95%)'*
POPULATION	Patients with EGFR Exon20ins mutated NSCLC	The patient cohort from the CHRYSALIS trial, comprising the efficacy analysis set (EAS), N=114, presented in Section B.2.6 of the original company submission was used to derive data for amivantamab for the analyses, as per the relevant marketing authorisation. In order to compare patients from CHRYSALIS Cohort D+ with similar patients from the US and PHE datasets, the same inclusion and exclusion criteria used for the CHRYSALIS trial were used to identify patients in the RWE datasets where possible. The inclusion and exclusion criteria applied to	Accuracy	All patients in the study were confirmed to have the EGFR Exon20ins mutation. Therefore, all included patients were from a relevant population. In the US sources, primarily NGS was used to identify those with EGFR Exon20ins. A smaller proportion was identified using PCR. NGS is the gold standard approach.	Information not available.

		all RWE sources are presented in Appendix M of the original submission.			
POPULATION	Baseline characteristics	Baseline demographics and patient characteristics	Completeness	Information relating to missing data is summarised elsewhere in this response.	N/A
		Baseline demographics and patient characteristics	Accuracy	Baseline characteristics were consistent between sources and between CHRYSALIS and the US sources, and were deemed to be generalisable to UK practice.	N/A
OUTCOME	ORR PFS OS TTNT	Definitions for these outcomes are provided in the table above.	Accuracy	Means and confidence intervals are available for all analyses for key outcomes relevant to the decision problem and are presented in this response. Overall, results were consistent across methodologies and data sources.	Information not available.

Table 11: Data relevance

Item	Information	Response
POPULATION	*Describe the extent to which the analytical sample reflects the target population. This should consider any data exclusions (for example, because of missing data on key prognostic variables).*	The baseline characteristics of the US RWE cohort were validated by UK clinical experts as generalisable to those seen in UK clinical practice.[11] LOTs with missing ECOG values were excluded from the analysis and no left truncation was applied to the data. Treatment lines with missing ECOG were excluded from the analysis to reduce uncertainty, and as the large sample size from the US sources allowed for this without a detrimental decrease in the number of LOTs included in the analysis. Only treatment lines where patients received EGFR Exon20ins testing prior to treatment were included.
CARE SETTING	*Describe how well the care settings reflect routine care in the NHS.*	Both the baseline characteristics and outcomes from the US pooled analysis have been validated with UK clinicians as generalisable to UK clinical practice. Also, the similarity of the baseline characteristics and outcomes between the US and PHE datasets supports the conclusion that the data accurately reflects clinical practice in the NHS as PHE data were collected from patients in the NHS directly.
TREATMENT PATHWAY	*Describe how the treatment pathways experienced by people in the data reflects routine care pathways in the NHS (including any diagnostic tests).*	The percentage of LOT from each treatment class in the US RWE and PHE data sets, the latter of which is directly reflective of routine care in the NHS are shown below.

Treatment class	US RWE	PHE
IO agents	[redacted]	[redacted]
TKIs	[redacted]	[redacted]
Non-platinum chemotherapy	[redacted]	[redacted]

		<table><tr><td>**Platinum-based chemotherapy**</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>**Other***</td><td>[redacted]</td><td>[redacted]</td></tr></table> *'Other' includes clinical study drugs, ALK inhibitors, multi-kinase inhibitors, anti-EGFR monoclonal antibodies, mTOR inhibitors, and oestrogen modulators for the US RWE and poziotinib for PHE. Overall, these are considered in this category as they are investigational drugs and drugs not considered to be part of the standard of care (e.g., breast cancer drugs). Although the treatment class distributions differ between the US and PHE RWE data sources, outcomes from the US RWE were considered generalisable to the UK patient population, indicating that the outcomes achieved when receiving US SoC are similar to what would be expected in UK practice.[11] **Diagnostic Testing** Only treatment lines where patients with NSCLC received EGFR Exon20ins testing prior to treatment were included, ensuring that treatment was reflective of clinical practice once physicians were aware that a patient had an EGFR Exon20ins mutation in NSCLC, and to avoid immortal time bias. Primarily NGS was used to identify those with EGFR Exon20ins. A smaller proportion was identified using PCR. Those with advanced NSCLC were identified based on diagnosis by their provider, as checked by curator.
AVAILABILITY OF KEY STUDY ELEMENTS	*Note how the dataset met the requirements of the research question in terms of availability of the necessary data variables including key population eligibility criteria, outcomes, intervention and covariates (including confounders and effect modifiers).*	**Population** Data were collected from patients with advanced *EGFR*-mutated NSCLC with Exon20ins following platinum-based therapy at 2L+, to align with the marketing authorisation for amivantamab and the indication of relevance for this submission.

		Eligibility Criteria To compare patients from CHRYSALIS Cohort D+ with similar patients from the external data sources, the same inclusion and exclusion criteria were applied to all real-world data sources, where possible, depending on data availability. Patients from the real-world data sources that satisfied inclusion criteria at multiple times during their follow-up contributed to the analysis with more than one line of therapy. **Outcomes** Data for ORR, PFS, OS and TTNT were all available from the US RWE data source. **Intervention** Available data on all anti-cancer treatments provided to patients were included in the dataset. **Covariates** To account for differences in patient populations between the CHRYSALIS trial and the RWE data sources, the adjusted treatment comparison adjusted for key prognostic variables and baseline characteristics, which were identified *a priori* by an SLR and validated by clinical experts.[13] The following covariates were considered: [redacted]

		The covariates actually adjusted for in the US RWE data source were based on the confounders identified by the SLR, clinical expert opinion and data availability (i.e., that data from relevant data sources were available for that covariate, and that data were available for a sufficient sample size [at least five to nine events per confounder]), see Table 23 in Document B of the submission. Overall, UK clinical experts agreed that key prognostic factors had been considered in the analysis.
STUDY PERIOD	*State the extent to which the time period covered by the data provides relevant information to decisions. This should cover any important changes to care pathways (including tests) or background changes in outcome rates.*	Data were collected from the US sources between 15 December 2009–16 October 2020. Therefore, some data were not collected within a recent timeframe. However, this duration of data collection allowed for a robust sample size to be included in the analyses. In addition, as amivantamab was the first treatment targeting EGFR Exon20ins mutations in NSCLC to be licensed, it is not anticipated that treatment outcomes on SoC therapies would differ between 2009 and 2020 as SoC outcomes continue to be sub-optimal for this patient population, as demonstrated consistently in the results of the adjusted comparison.
TIMING OF MEASUREMENTS	*Describe whether the timing of measurements meet the needs of the research question.*	PFS – Unlike in a clinical trial, there was no regular scanning. Scanning was according to clinician determined schedule.[14] OS – Data were collected from obituaries, the EHR or government records (e.g., from the Social Security Administration).[15] TTNT – This was based on clinical practice in changing treatments. ORR – Unlike in a clinical trial, there was no regular scanning. Scanning was according to a clinician determined schedule.[16]

FOLLOW UP	*Note how the follow-up period available in the dataset is sufficient for assessing the outcomes.*	The follow-up period was not calculated.
SAMPLE SIZE	*Provide the sample size of the target population in the dataset and demonstrate that it is adequate to generate robust results.*	Once LOTs with missing ECOG scores had been excluded, the US RWE cohort was made up of [redacted] LOTs. Given the rarity of EGFR Exon20ins NSCLC, data from a population of this size provides valuable information about the SoC treatments received by these patients.

Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 16 September 2022. Please submit via NICE Docs.

Appendix 3: Additional adjusted comparison results for CHRYSALIS vs US RWE

Adjusted comparisons using IPW ATT methodology as described in Section B.2.9 of Document B in the original submission for amivantamab using CHRYSALIS data versus the US RWE were conducted individually for the three datasets (Flatiron, ConcertaAI and COTA) as well as for the pooled cohort.
Multiple imputation methodology was implemented to provide a sensitivity analysis accounting for missing data. The distribution of the partially observed covariates (specifically in this case, only number of metastatic locations) was estimated given the fully observed covariates (all other covariates included in the base case) and used to impute the missing observations for number of metastatic locations.

Multiple imputation was only conducted for the pooled cohort and Flatiron. For ConcertAI and COTA, any results with an imputed dataset yield the same results as with the original dataset. In the case of ConcertAI, the source did not have any observation with missing values. For COTA, the inclusion of all covariates as in the base case led to strongly unbalanced covariates between treatment arms after ATT-weighting, possibly reflecting the smaller sample size relative to the pooled case. A balance between covariates of higher relevance was reached only when including for adjustment; prior lines of treatment, age, brain metastasis, and ECOG PS. As the covariate number of metastatic locations was not included for ATT-adjustment for COTA, its missing observations did not play any role in the sensitivity analysis presented here.

Results for each endpoint are generally consistent across the 3 datasets (Flatiron, ConcertaAI and COTA) individually and when pooled. Table 12 presents the key results (i.e. endpoints that inform the economic model) in the subgroup of patients in the US RWE cohort excluding EGFR TKIs. In summary:

- OS: the HRs consistently show that amivantamab statistically significantly reduces the risk of death when compared to the RWE cohorts across the datasets. This benefit is maintained when multiple imputation for missing data is applied
- PFS: similarly, the HRs show that amivantamab statistically significantly reduces the risk of progression as determined by IRC when compared to the RWE cohorts across the datasets. This benefit is also maintained when multiple imputation for missing data is applied.

Table 12: Adjusted comparisons results (HRs, 95% confidence intervals and p values) including additional sensitivity analyses requested by the ERG and AC

ATT-adjusted results	AMI versus Pooled US	AMI versus Flatiron	AMI versus ConcertAI	AMI versus COTA[a]
OS (March 2022)				
No imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]
PFS IRC				
No imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]

With imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]

[a] For the comparison of CHRYSALIS versus COTA, covariates up to and including ECOG were adjusted for in the analyses.

Additional adjusted comparison results using IPW ATT methodology for CHRYSALIS versus US RWE are provide in Table 13 below, covering the full population and the subgroup of patients excluding TKIs. Results are presented with and without imputation. Overall, the results demonstrate consistency across endpoints and data sources irrespective of the application of imputation and/or the inclusion/exclusion of TKIs.

Table 13: Additional adjusted comparison results including additional sensitivity analyses as requested by the ERG and AC

ATT-adjusted results	AMI versus Pooled US	AMI versus Flatiron	AMI versus ConcertAI	AMI versus COTA[a]
OS (March 2021)				
No imputation, including TKIs	[redacted]	[redacted]	[redacted]	[redacted]
No imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, including TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]
OS (March 2022)				
No imputation, including TKIs	[redacted]	[redacted]	[redacted]	[redacted]
No imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, including TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]
PFS INV				
No imputation, including TKIs	[redacted]	[redacted]	[redacted]	[redacted]

No imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, including TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]
PFS IRC				
No imputation, including TKIs	[redacted]	[redacted]	[redacted]	[redacted]
No imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, including TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]
TTNT				
No imputation, including TKIs	[redacted]	[redacted]	[redacted]	[redacted]
No imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, including TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, excluding TKIs	[redacted]	[redacted]	[redacted]	[redacted]

[a] For the comparison of CHRYSALIS versus COTA, covariates up to and including ECOG were adjusted for in the analyses. [b] Only three events were observed in the PC arm. [c] Numerical benefit for amivantamab versus SoC, but this did not reach statistical significance.
Abbreviations: IRC: independent review committee; INV: investigator-assessed; PFS: progression-free survival; OS: overall survival; TKIs: tyrosine kinase inhibitors; TTNT: time to next treatment.

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Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 16 September 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	EGFR Positive UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a
Name of commentator person completing form:	[redacted]
Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Unmet need - this is massive and should have been much more strongly registered.
2	Small population who are greatly underserved and are outliers in the EGFR community
3	The negative impact of knowing a treatment is available and not being able to access it. Both drugs are approved and used in other countries yet in the UK patients with Exon 20 ins are denied this opportunity
4	In the absence of a well known and followed standard of care these patients, whose diagnosis is often missed, are placed on a variety of treatment pathways which have limited efficacy and often have a high toxicity.
5	The emotional, social and economic impact on quality life when living with EGFR Positive lung cancer has not been registered
6	The positive impact of having access to a targeted therapy that prolongs their life and positively impacts the quality of their life. This treatment is a game changer for these patients and not enough emphasis has been made of this.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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NICE National Institute for Health and Care Excellence

Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Roy Castle Lung Cancer Foundation
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]
Comment number	**Comments**

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Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are disappointed that the Appraisal Committee Decision is not to recommend this therapy in this indication. This would be the first to be NICE recommended for treating this highly selected group of patients, with EGFR exon 20 insertion mutation-positive, advanced non small cell lung cancer. As acknowledged in the ACD, indirect comparisons using real world evidence suggest that Amivantamab, in this indication, increases how long people live and how long before their cancer gets worse. This is of obvious importance in this patient group. As further acknowledged, this therapy does meet the criteria of a life extending treatment, at end of life. These patients do not have time to wait. As such, we would encourage discussion with the manufacturer around cost and potential for use in the Cancer Drugs Fund, whilst further data becomes available.

Insert extra rows as needed

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy (review of TA10729) [ID3836]

ERG critique of company response to ACD

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre+ (UMC+)

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Date completed 2124/06/2022

Source of funding: This report was commissioned by the National Institute for Health Research (NIHR) Evidence Synthesis Programme as project number STA 13/44/06.

Declared competing interests of the authors None

Acknowledgements None

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Howick J, Witlox W, McDermott K, Wijnen B, Danopoulos E, Otten T, Ahmadu C, Otten T, Duffy S, Perry M, Westwood M, Armstrong N, Wolff R, Joore M, Kleijnen J. Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy (review of TA10729) [ID3836]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2022.

Contributions of authors

Jeremy Howick acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Willem Witlox and Ben Wijnen acted as health economic project leads, critiqued the company's economic evaluation, and contributed to the writing of the report. Thomas Otten, Charlotte Ahmadu, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott, Evan Danopoulos, Mark Perry, and Marie Westwood acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Robert Wolff and Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AACR	American Association for Cancer Research
AE	Adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AIFA	Agenzia Italiana del Farmaco
AMI	Amivantamab
ASCO	American Society of Clinical Oncology
ATT	Average treatment effect among the treated
AWMSG	All Wales Medicines Strategy Group
BAG	Bundesamt für Gesundheit
BICR	Blinded independent committee review assessed
BMI	Body mass index
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
CADTH	Canadian Agency for drugs and Technologies in Health
CBR	Clinical benefit rate
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Clinical Trials
CI	Confidence interval
cm	Centimetre
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
DARE	Database of Abstracts of Reviews of Effects
DFS	Disease free survival
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL 5-dimensions 5-levels
EQ-5D-5L VAS	EuroQol-5 dimensions 5-levels visual analogue score
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
Exon20ins	Exon 20 insertion mutations
FE	Fixing errors
FinCCHTA	Finnish Coordinating Center for Health Technology Assessment
FDA	Food and Drugs Administration
FV	Fixing violations
G-BA	Gemeinsamer Bundesausschuss
HAS	Haute Autorité de Santé
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life

HTA	Health technology assessment
IASLC	International Association for the Study of Lung Cancer
ICER	Incremental cost-effectiveness ratio
iDFS	Invasive disease-free survival
ILD	Interstitial lung disease
INV	Investigator-assessed
IPD	Individual participant data
IPW	Inverse probability weighting
IRR	Infusion related reaction
IO	Immuno-oncology
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
kg	Kilogram
KM	Kaplan-Meier
LOT	Line of therapy
LS	Least squares
LY	Life year
mg	Milligram
MET	Mesenchymal epithelial transition
MHRA	Medicines and Healthcare Products Regulatory Agency
MJ	Matters of judgement
MSCBS	Ministerio de Sanidad, Consumo y Bienestar Social
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NCPE	National Centre for Pharmacoeconomics
NCRAS	National Cancer Registration and Analysis Service
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIPH	Norwegian Institute of Public Health
NR	Not reported
NSCLC	Non-small-cell lung cancer
NSCLC-SAQ	Non-small-cell lung cancer Symptom Assessment Questionnaire
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
pCR	Pathological complete response
PD	Progressed disease
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PHE	Public Health England
PPS	Post-progression survival
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome

PSA	Probabilistic sensitivity analysis
PSM	Propensity score matching
PSSRU	Personal Social Services Research Unit
Pt	Platinum
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RID	Residual invasive disease
RP2D	Recommended Phase 2 dose
RWD	Real world data
RWE	Real world evidence
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SCLC	Small cell lung cancer
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMD	Standardised mean difference
SoC	Standard of Care
SoD	Sum of diameters
STM	State transition model
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTF	Time to treatment failure
TTNT	Time to next treatment
UK	United Kingdom
US	United States
VAS	Visual analogue scale

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Section 1 – The reporting of the real-world evidence for the comparator arm

The company provided a response[1] to page 9 of the ACD:[2] *"the committee considered that the company had not provided enough information on data provenance, data accuracy and data suitability, and had not explored the effect of missing data. The committee concluded that the way the company had chosen and used real-world evidence was associated with several areas of uncertainty."*

In particular, the company have responded to the following statements in the ACD:[2]

- *"The committee noted that the company could have used well-validated real-world evidence checklists and reporting tools (such as the RECORD-PE checklist or the STaRT-RWE template)."*

This was by completing the DataSAT checklist, which is recommended by NICE, and was provided in Appendix 2 of the company response to the ACD.[1]

- *"The company could have done a sensitivity analysis using a multiple imputation approach to assess the impact of missing data."*

This was by conducting the following sensitivity analyses (see Table 12 of the company response to the ACD):

  - Amivantamab versus pooled US RWE with imputation for missing values
  - Amivantamab versus pooled US RWE with imputation for missing values and with EGFR tyrosine kinase inhibitors (TKIs) excluded
  - Amivantamab versus Flatiron with imputation for missing values
  - Amivantamab versus Flatiron with imputation for missing values and with EGFR TKIs excluded

The company stated that imputation was not necessary for ConcertAI because there were no missing values and not performed for missing data on number of metastatic locations for COTA because: *"…adjusting for all covariates including this covariate led to a large degree of imbalance…"*.[1] Baseline data showing number missing were presented in Table 7 of the company response to the ACD, excluding number of metastatic locations, for which data were missing from Flatiron ([redacted]) and COTA ([redacted]) In fact, it was reported in Appendix 3 that the only missing data that were imputed were number of metastatic locations and only for the pooled cohort and Flatiron. It was also reported in Appendix 3 that the imbalance referred to was between treatment arms after Average Treatment Effect on the Treated (ATT) propensity score (PS) weighting. This meant that adjustment with imputation had to be limited to the covariates: prior lines of treatment, age, brain metastasis, and ECOG PS.

The company claimed that the results of these analyses, including with and without EGFR TKIs, demonstrated consistency irrespective of imputation or EGFR TKI presence.

- *"It could also have reduced uncertainty by providing further detail on how it chose data sources and assessed their suitability. In particular, for each of the 3 US real-world evidence sources in the company base case, further information to reduce uncertainty could have included:*
  - *a description of each data source and the number of people included"*
  - *"a description of the missing data and the number of people excluded from the analyses at each step of filtering (for example, how many people were filtered because of each eligibility criterion or because of missing data on key confounding variables)"*

This was by providing the eligibility criteria for each of the three data sources, ConcertAI, COTA and Flatiron (see Table 1 of the company response to ACD) and an explanation of the methodology by which lines of therapy (LOTs) were determined, which resulted in the inclusion of [redacted] patients representing [redacted] LOTs.[1] Table 6 in the company response to the ACD shows the criteria used for including LOTs and the result of the stepwise process of their application. The company also stated:[1] *"Additionally, a further criteria was applied for the analysis informing the Company Submission: exclusion of LOTs for patients who were not diagnosed with NSCLC with EGFR Exon20ins at the time of LOT start, meaning that [redacted] LOTs were included in the final analysis set of interest."*

- *"a description of the provenance of the data source"*
- *"further information on key study variables and outcomes, including details on data availability and completeness, how they were measured and derived from the data, whether any linkage to external data sources was included and an assessment of accuracy"*
- *"the time period when the information was collected for each variable in the real-world evidence, defined in relation to the treatment start date."*

The response to these three items was to refer to the DataSAT checklist in Appendix 2.[1]

- *"The committee also noted that a full study protocol for each of the real-world evidence sources according to the NICE real-world evidence framework requirements should be provided."*

The protocol for the RWE study comparing CHRYSALIS to the three US data sources was included in the reference pack.

ERG comment:

The company have responded appropriately to the ACD in providing the DataSAT checklist, the explanation of how patients/LOTs were selected from the RWD, the extent of missing data and the additional analyses based on EGFR TKI inclusion and number of lines of metastatic treatment imputation.

Given the conclusion expressed in the ACD that "…EGFR TKIs were not an appropriate comparator." (p. 6), the most relevant results are those where EGFR TKIs have been excluded from the RWD.

The company stated that they had responded to the statement in the ACD that the company *"…could also have reduced uncertainty by providing further detail on how it chose data sources…"* (p. 9) However, although they provided eligibility criteria for the data sources that were used, which indicated their suitability, they did not provide any information as to how those sources were chosen from the pool of all potential data sources. Although the company completed the DataSAT checklist, this was not used to affect in any way the choice of data source and, as stated in the ERG report, a full search for all relevant studies has still not been conducted.

The eligibility criteria shown in Table 1 of the company response to the ACD show general conformity between the three data sources, although they do reveal some potential selection bias due to excluding patients with "*insufficient EHR data"* for ConcertAI and COTA. The DataSAT RWE checklist also reveals differences between the data sources in terms of care setting: patients in Flatiron and Concert AI were "*primarily in the community oncology setting*" whereas 79% those in COTA were treated at academic medical centres, the remainder in the community. There are also differences in baseline characteristics between the data sources, particularly between COTA and the other two in brain metastases (more common in COTA), ECOG PS (higher in COTA), number of metastatic locations

(more in COTA). These baseline characteristics of COTA also appeared to more dissimilar and those of Flatiron most similar to those in the amivantamab data (CHRYSALIS). Nevertheless, the results for the pooled analysis, which was used in the base case, were conservative (higher HR) for all outcomes (OS, PFS and TTNT) relative to all those based on any single data source in most cases. Using the latest (March 2022) data cut-off and excluding EGFR TKIs (the most relevant scenario) and PFS IRC, the only exception was for PFS: pooled, regardless of imputation ([redacted]), COTA ([redacted]).

Section 2 – The stigma associated with NSCLC with EGFR Exon20ins

ERG comment: None.

Section 3 – The most appropriate approach for amivantamab time on treatment

ERG comment:

No compelling new arguments or evidence provided. Hence, the ERG perspective as described in the ERG report remains unchanged.

Section 4 – The addition of a scenario exploring the impact of diagnostic testing costs

As requested by the committee, the company conducted a scenario analysis including the cost of testing for EGFR Exon20ins in NSCLC at £550 per patient with NSCLC with EGFR Exon20ins. This scenario analysis slightly increased their base-case ICER to £28,733.

ERG comment:

The company have responded appropriately to the ACD in providing the scenario analysis including the cost of testing for EGFR Exon20ins in NSCLC at £550 per patient with NSCLC with EGFR Exon20ins. The ERG incorporated this analysis in its ERG base-case.

Section 5 – Revised base-case cost-effectiveness analysis and revised PAS

The company updated the PAS for amivantamab and presented a revised company base case, accommodating the following assumptions as preferred by the committee:

- excluding EGFR TKIs from the blended comparator arm
- using the inverse probability weighting method for the indirect treatment comparison
- using utility values from TA713
- using parametric modelling to represent survival in the blended comparator arm
- excluding treatment waning

Contrary to the preferences of the committee, however, the company base-case assumes that time on treatment for amivantamab equals PFS.

ERG comment:

The ERG appreciates that the company incorporated most of the committee preferred assumptions in their new base-case. However, the ERG considers that, in line with the preferred committee assumptions, it is appropriate to model time on treatment based on the CHRYSALIS time to treatment discontinuation data, with the exponential curve (as the best statistical fit) applied in its ERG base-case. In addition, as commented in section 4 above, the ERG incorporated the addition of testing costs for EGFR Exon20ins in NSCLC at £550 per patient with NSCLC with EGFR Exon20ins in its base-case.

Section 6 – Factual inaccuracies

The company explained that the reason that only n=114 patients were included in the efficacy population was that not all patients had received ≥3 disease assessments.

ERG comment:

The criterion regarding number of disease assessment was already included in the ERG report. Therefore, this does not provide any further clarification and it remains unclear as to why this number of assessments was a criterion.

Section 7 – Confidentiality highlighting errors

ERG comment: none.

Table 1: Company's updated base-case (and updated PAS), and updated ERG base-case.

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's updated deterministic base-case (including new PAS)					
Amivantamab	[redacted]	[redacted]			
UK SoC	[redacted]	[redacted]	[redacted]	[redacted]	£27,766
ToT amivantamab based on CHRYSALIS time to treatment discontinuation - exponential					
Amivantamab	[redacted]	[redacted]			
UK SoC	[redacted]	[redacted]	[redacted]	[redacted]	£40,909
Addition of testing costs for EGFR Exon20ins in NSCLC at £550 per patient with NSCLC with EGFR Exon20ins					
Amivantamab	[redacted]	[redacted]			
UK SoC	[redacted]	[redacted]	[redacted]	[redacted]	£28,733
Deterministic ERG base-case (including new PAS)					
Amivantamab	[redacted]	[redacted]			
UK SoC	[redacted]	[redacted]	[redacted]	[redacted]	£41,876
Probabilistic ERG base-case (including new PAS)					
Amivantamab	[redacted]	[redacted]			
UK SoC	[redacted]	[redacted]	[redacted]	[redacted]	£40,681

ERG = evidence review group, HRQoL = health-related quality of life, ICER = incremental cost-effectiveness ratio, IPW = inverse probability weighting, PSM = propensity score matching, QALY = quality-adjusted life year, TTNT = time to next treatment, UK SoC = United Kingdom standard of care.

References

[1] National Institute for Health and Care Excellence. *Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]. ACD stakeholder comments. Janssen-Cilag Ltd*. London: National Institute for Health and Care Excellence, 2022

[2] National Institute for Health and Care Excellence. *Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy. Appraisal consultation document*. London: National Institute for Health and Care Excellence, 2022